EXHIBIT C

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UNITED STATES DEPARTMENT OF COMMERCE
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07/644,967 01/22/91 COLLINS M 25.83503

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1807 2

03/12/92

☒ This application has been examined ☒ Responsive to communication filed on 1/22/91 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ ____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.

   Of the above, claims 24 is withdrawn from consideration.

2. ☐ Claims ____ have been cancelled.
3. ☐ Claims ____ are allowed.
4. ☒ Claims 1-23 are rejected.
5. ☐ Claims ____ are objected to.
6. ☒ Claims 24 is subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on ____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ____; filed on ____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Serial Number 07/644,967
Art Unit 1807

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 180 Art Unit 1807.

Examiner notes that in E.I. du Pont de Nemours & Co. v. Cetus Corp., 19 USPQ2d 1174 at 1185 (N.D.Ca. 1991), the court indicated that grant proposals to the NIH and NSF were prior art due to the requirements of the Freedom of Information Act (see 45 C.F.R. §5.1 et seq. and §612 et seq.). This may be of some interest to applicants in satisfying 37 C.F.R. 1.56.

Applicants are requested to look over the specification and correct any minor errors.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-23, drawn to a method of nucleic acid amplification, classified in Class 435, subclass 6 and 91.

II. Claim 24, drawn to an apparatus and measuring device, classified in Class 435, subclass 291 & 293.

The inventions are distinct, each from the other because of the following reasons: Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP 806.05(e)). In this case the process as claimed can be practiced by hand as pointed out in the disclosure.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and different classification, as well as the fact that the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Anthony J. Januik on January 4, 1990, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in responding to this Office action. Claim 24 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants have indicated that the instant application is a continuation of 07/136,920.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and others recite "support capable of specifically associating with the target under binding conditions" which is vague and indefinite functional language describing a chemical moiety by what it does rather than by what it is structurally; therefore it is impossible to know what is and what is not claimed. Claim 6 recites "probe" which is vague and indefinite: do applicants intend a specific nucleic acid sequence which will probe through hybridization or is something else intended? Claim 6 also is phrased in functional language. Claim 10 recites "transcriptase" which is vague and indefinite; was "reverse transcriptase" contemplated? Claim 11 and others recite "non-specific oligonucleotide primer" which is vague and indefinite. Claim 13 and others recite "substantially separating" which is vague and indefinite. Claim 21 recites "capable of binding to a retrievable support" which is vague and indefinite functional language. The claims also recite "retrievable support" but it is not clear what support would not be retrievable; thus it is confusing. It also recites "reagents adapted to be applied to said removal product" which is vague and indefinite. Claim 22 (and claim 23 since it depends on claim 22) refer to the "method of claim

21", but claim 21 is a kit claim corresponding to various compositions of matter: it is not a method claim. This makes claims 22 and 23 confusing. Claim 23 recites "capable of interacting with a magnetic field" which is vague and indefinite: in light of the known ability of any carbon, nitrogen, or hydrogen containing compound to interact with a magnetic field (e.g. NMR) it is not clear what applicants are describing.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-23 are rejected under 35 U.S.C. 103 as being unpatentable over any one of Mullis, Mullis et al., or Mullis et al. (ref. R) when taken with any one of Moss et al., Wood et al., Noyes et al., Shih et al., Stabinsky or Engelhardt et al. and taken further in view of Ranki et al. or Josephson or Schroder if necessary.

The primary references all teach DNA amplification and point out the great value of this method for improved sensitivity as well as improved ability to isolate specific nucleotide sequences. The primary references do not specifically teach nucleic acid affinity chromatography prior to the amplification reaction. The secondary references all teach the well known method of affinity chromatography, both with nucleic acid attached to a support (direct hybridization) as well as through ligands attached to one strand of the nucleic acid (e.g. biotin-avidin). The secondary references teach the value of affinity chromatography in its ability to isolate specific

nucleotide sequences and remove unwanted sequences which would interfere with later usefulness of the sequences. The secondary references also teach the greater efficiency of hybridization and improved sensitivity of an affinity purified sample compared to a non-purified sample (e.g. Moss et al. figure 3) although this fact would be well known to one of ordinary skill in the art. It would be obvious for one of ordinary skill in the art to combine the teachings of the primary references which show improved sensitivity and improved ability to purify a sequence with the secondary references which teach a method providing improved ability to purify a sequence and improved sensitivity since the methods are all directed to the same result and one of ordinary skill would expect an improvement in results.

In regard to claims directed to association with a "probe": it is not clear what applicants mean by this language (see supra); however, it appears to be the well known method of sandwich hybridization (see Ranki et al., this reference has not been provided, it was provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with it) which also claims increased sensitivity and greater ability to isolate specific sequences. In regards to "non-specific oligonucleotide primer": it is not clear what applicants mean by this language (see supra); however, it appears that applicants are simply referring to the well known method of random primer polymerization which is used to label probes. This method is well known not only as an efficient method of making a second copy (into which labeled nucleotides can be added) but is also more efficient than using a single primer. One of ordinary skill in the art would have known this technique and would have been motivated to use it since it makes a second strand thereby doubling the number of copies to be amplified. In regards to the use of a "bead capable of interacting with a magnetic field": it is not clear what applicants mean by this language (see supra); however, it appears to be the well known method of Josephson and Schroder for magnetic separations (these references have not been provided, they were provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with them). In regards to the kit claims: it would have been obvious to one of ordinary skill in the art to package all of the components in a kit for the convenience of practitioners of the method.

To clarify this rejection, it is examiner's position that applicants simply combined the well known method of nucleic acid amplification with the equally well known method of affinity chromatography to produce a result which would have been expected and with sufficient motivation to make the combination. Thus applicants invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

No claim is allowed.

This is a continuation of applicant's earlier application S.N. 07/136,920. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Examiner has not provided copies of any of the references cited in this Office Action because they were provided in earlier Office Actions on the parent case.

An inquiry concerning this communication should be directed to Scott A. Chambers, Ph.D. at telephone number 703-308-3885.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Scott A. Chambers
Patent Examiner
Art Unit 1807

MARGARET MOSKOWITZ
SUPERVISORY PATENT EXAMINER
GROUP 180

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

SERIAL NO. 07/644,967 | GROUP ART UNIT 1807 | ATTACHMENT TO PAPER NUMBER 2

NOTICE OF REFERENCES CITED

APPLICANT(S) Collins et al.

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
V	A	4,672,040	June 9/87	Josephson	436	526	June 28/85
V	B	4,471,058	Sep. 11/84	Smith et al.	436	518	
V	C	4,486,539	Dec. 4/84	Ranki et al	436	504	
V	D	4,687,748	Aug 18/87	Schröder	435	526	Mar 23/83
V	E	4,751,177	June 14/88	Stalinski	435	6	June 13/85
V	F	4,683,195	July 28/87	Mullis et al	435	6	Mar 28/85
V	G	4,683,202	July 28/87	Mullis	435	91	Mar 28/85
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
V	L	0097373	04/01/84	EP	Engelhardt	435	6		
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

V R Mullis et al. Cold Spring Harbor Symposia on Quantitative Biology 55 (1986) Cold Spring Harbor Press; Cold Spring Harbor NY p 263-73

V S Moss et al. Journal of Biological Chem 256: 12655-58 (1981)

V T Shih et al Biochemistry 13(6): 3411-18 (1974)

V U Noyes et al; Cell 5 301-11 (1975)

EXAMINER [signature] DATE 3/11/92

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
07/644,967	1807	2

APPLICANT(S): Collins et al.

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

√	R	Wood et al.; Journal Biol Chem 252:457-63 (1977)
	S	
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	U	

EXAMINER: [signature] DATE: 3/11/92

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

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